A final synopsis on the topic

SYNTHESIS AND CHARACTERIZATION OF BIOLOGICALLY ACTIVE NOVEL ORGANIC MOLECULES

Submitted to the

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For the degree of

DOCTOR OF PHILOSOPHY IN CHEMISTRY

Submitted by

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RESEARCH GUIDE IN CHEMISTRY

PRINCIPAL
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DIST. OSMANABAD

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"SYNTHESIS & CHARACTERIZATION OF BIOLOGICALLY ACTIVE NOVEL ORGANIC MOLECULES"

The thesis consist of five chapters, the description of each chapter is as follows.

Chapter 1:- Introduction

The present work entitled "SYNTHESIS & CHARACTERIZATION OF BIOLOGICALLY ACTIVE NOVEL ORGANIC MOLECULES" illustrate the synthesis of different biologically active organic molecules ranging from different aryl and hetero aryl compounds.

Keeping in view the importance of these organic molecules, we have planned the synthesis of a series of compounds containing biologically important pharmacophores, in addition all the synthesized compounds will be screened for their antibacterial activities, and few compounds will also screened for their anti-inflammatory and analgesic activities. Our present studies aims to develop certain organic molecules of sciff's bases, quinolines, isoquinolines and β-Amino carbonyl compounds family.

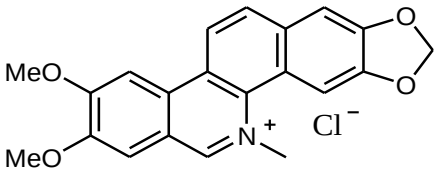
Compounds containing azomethine group (-C=N-) in the structure are known as sciff's bases, which are usually synthesized by the condensation of primory amines and active carbonyl groups. sciff's bases are important class of compounds in medicinal and pharmaceutical field.

One Interesting role of sciff's bases is as intermediate in the biologically important transamination reaction. Transamination is the process whereby an amino group is transferred from one molecule to another. In Living systems the amino group of an amino acid is transferred to the carbonyl group of another molecule. The sequence promoted by enzyme called trainees enzyme. The new amino acids are formed by this method. sciff's bases constitute one of the most active class of compound possessing diversified biological applications.

They show biological applications one including antibacterial[16], antifungal[2-6], antitumor activity[7, 8], antioxidant[9-10], anti- inflammatory[11], antihypertensive[12], anti-HIV[13], anti filarial[14], anticonvulsant[15], herbicidal, insecticidal, schistosomicidal and anthelmintic[16] activities. sciff's bases and their complexes have a variety of application in biological, clinical and an-alytical fields[1].

Tetrahydroquinoline derivatives are an important class of compounds in the field of pharmaceuticals and exhibit a wide spectrum of biological activities[17], including psychotropic

anti-inflammatory and estrogenic behaviour. In particular, isoquinolonic acids are found to possess a wide range of pharmacological activities[18]. Isoquinolonic acids are useful precursors for the total synthesis of naturally occurring phenanthridine alkaloids[19] such as nitidine chloride (**1**) , decumbenine B (**2**), corynoline (**3**), oxocorynoline (**4**) and epicorynoline (**5**) as well as indenoisoquinolines[20] possessing significant antitumor activity. Thus, the syntheses of these heterocyclic compounds are very important.



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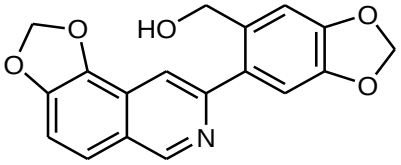

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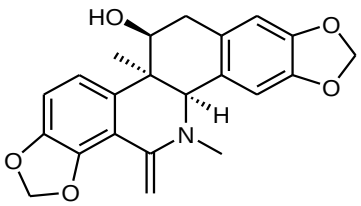
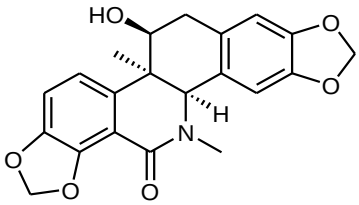
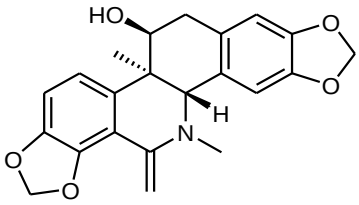


(+)- corynoline (3)



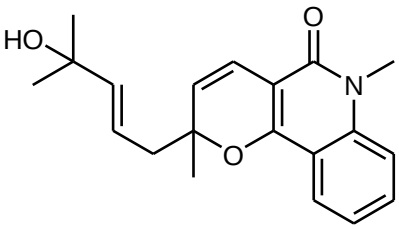
oxocorynoline (4)



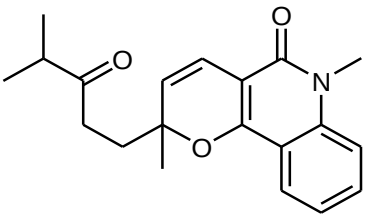
epicorynoline (5)

Tetrahydroisoquinolonic acid derivatives have attracted the attention of synthetic organic chemists due to their potential activity in the field of pharmaceuticals, and exhibit a wide spectrum of biological activities including psychotropic, anti-allergenic, anti-inflammatory and estrogenic behaviour[21].

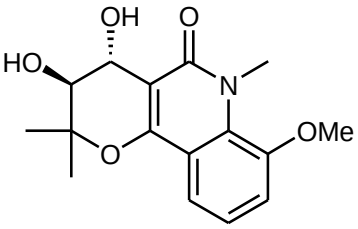
Pyrano- and furanoquinoline derivatives belongs to an important class of natural products and exhibit a wide spectrum of biological activities such as anti allergic, anti inflammatory, antipyretic, analgesic, anti platelet, psychotropic and estrogenic activity[22]. Many biologically active alkaloids like Simulenoline (**6**), Huajiaosimuline (**7**), Zanthodioline (**8**), Flindersine (**9**), Teclealbine (**10**) and Flindersiamine (**11**) contain pyranoquinoline and furanoquinoline moiety[22d-e, 23]. Hence, the synthesis of pyranoquinoline and furanoquinoline derivatives is of much current importance.



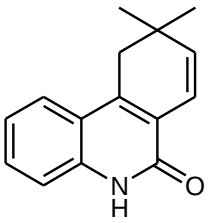
Simulenoline (6)



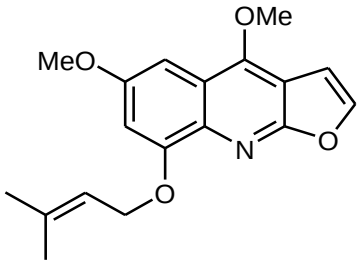
Huajiaosimuline (7)



Zanthodioline (8)



Flindersine (9)



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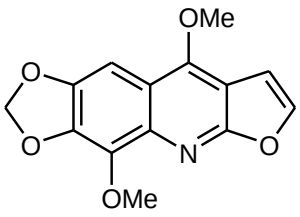
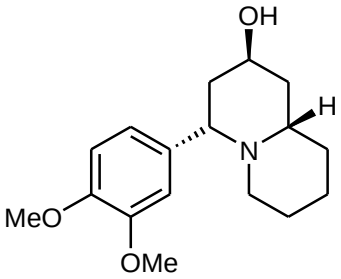


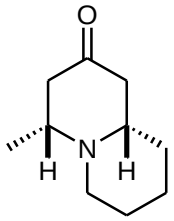
Flindersiamine(11)

β-amino carbonyl compounds are versatile intermediates for the synthesis of various complex natural products, antibiotics, β-amino alcohols and chiral auxiliaries[24]. The Aza-Michael reaction was used in the synthesis of various structurally complex piperidine and quinolizidine natural products, like (-)-Lasubine II (**12**), (+)-Myrtine (**13**), (-)-Epimyrtine (**14**)**, (+)-**Hyperaspine **(15),** (+)-Sedamine (**16**).

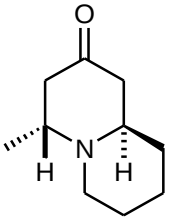
β -amino derivatives are attractive for their use as synthetic intermediates of anticancer agents, antibiotics and other drugs [25].



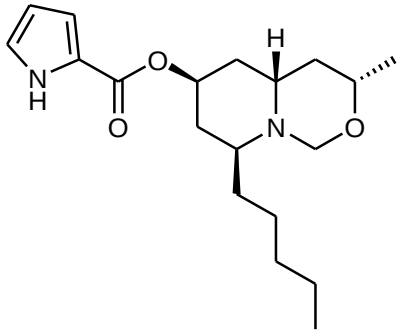
(-)-lasubine II (12)



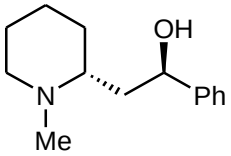
(+)-myrtine (13)



(-)-Epimyrtine (14)



(+)-hyperaspine (15)

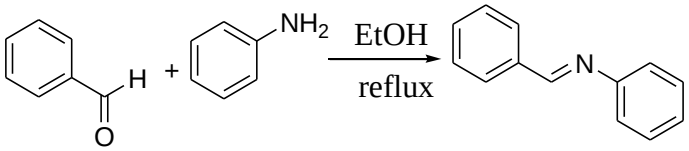


(+)-Sedamine (16)

Chapter 2:-Synthesis of sciff's bases.

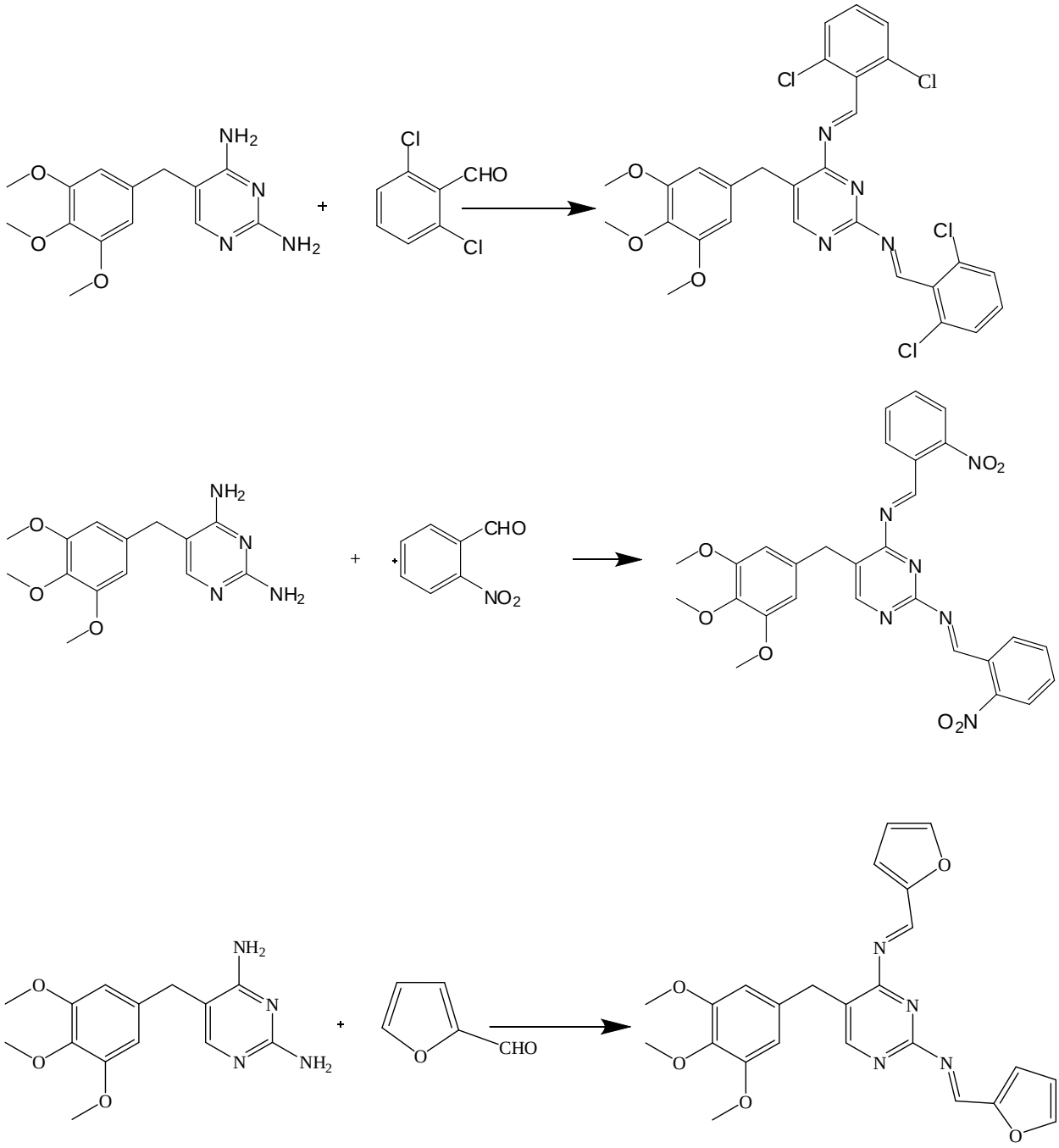
This chapter consist of different synthetic schemes of some novel sciff's bases with their experimental procedures and characterization. Here in this section we have synthesized new sciff's bases of different drug molecules. We have prepared these compounds by refluxing trimethoprime, cefadroxil and pyrimithiamine with different aldehydes in for appropriate time periods (Scheme 1).

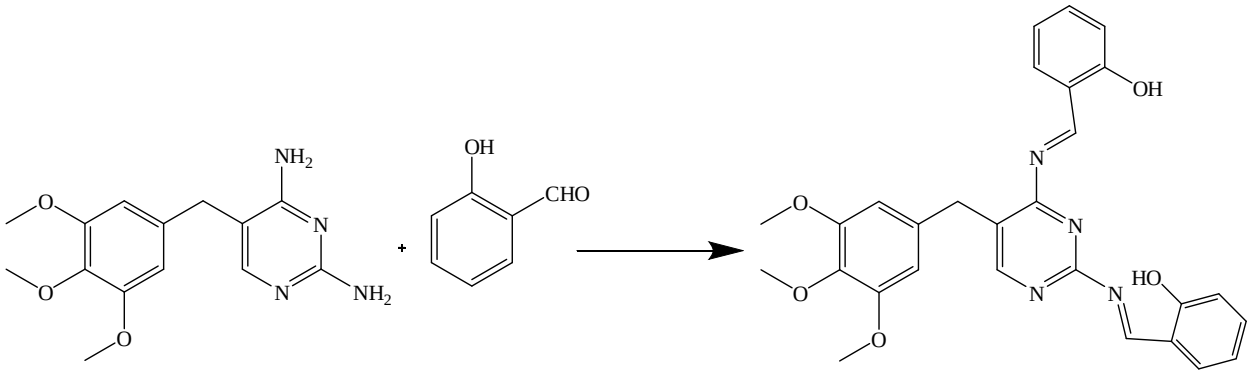
It consists of screening of the newly synthesized organic molecules. We are tried to screened these compounds for antibacterial activity, anti-inflammatory activity. It was observed that some of the newly synthesized compounds i.e Schiff bases of trimethoprime, cefadroxil and pyrimithiamine are found to be effective against microorganism.

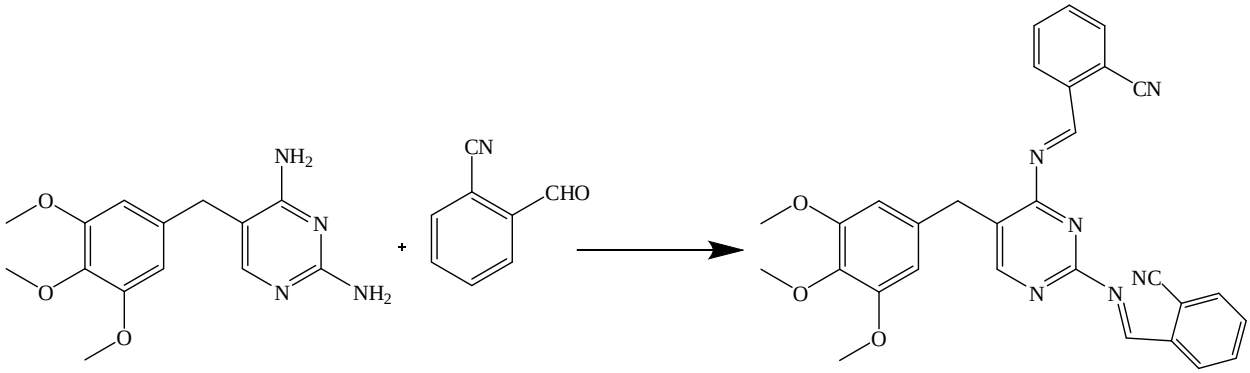


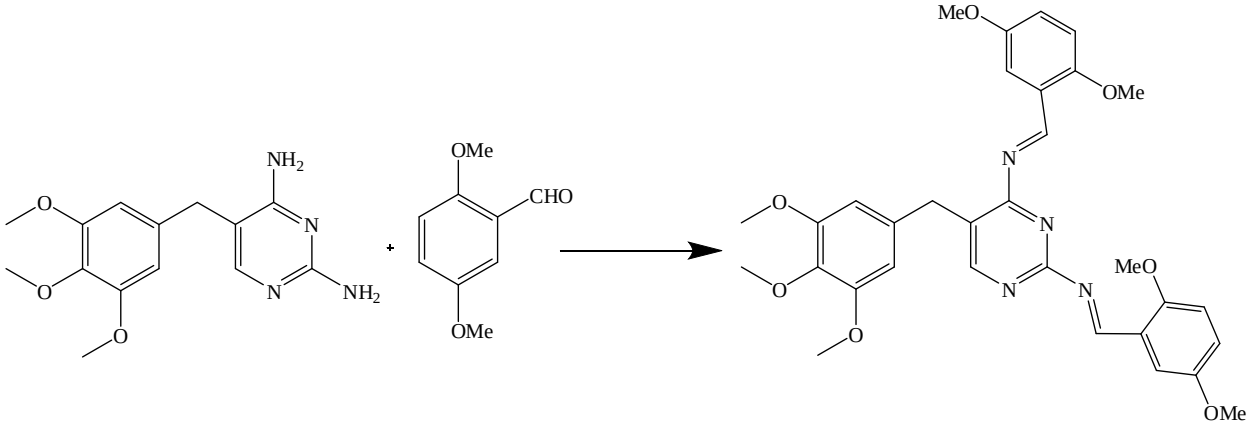
Scheme 1

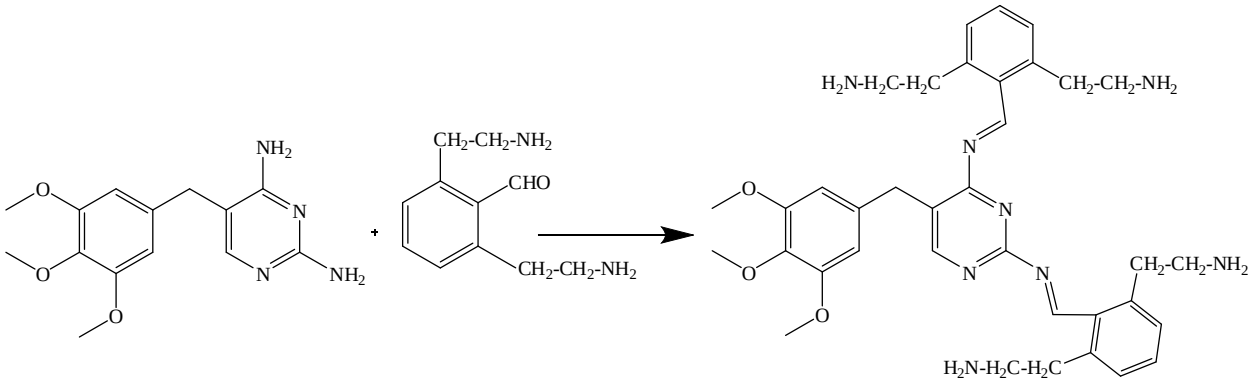
Trimethoprim



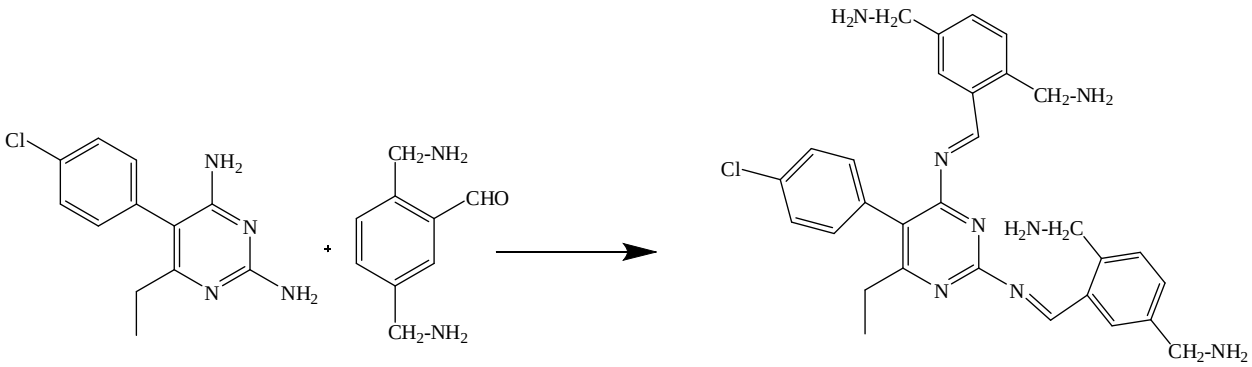


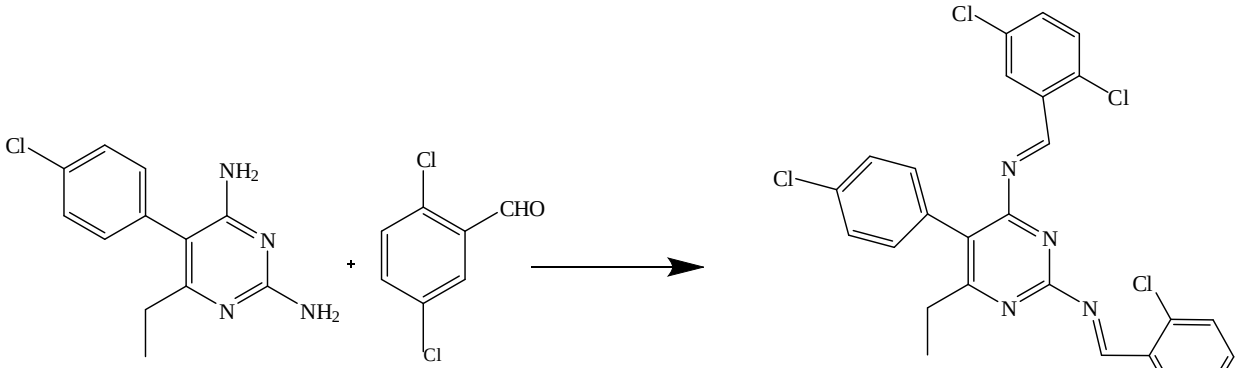


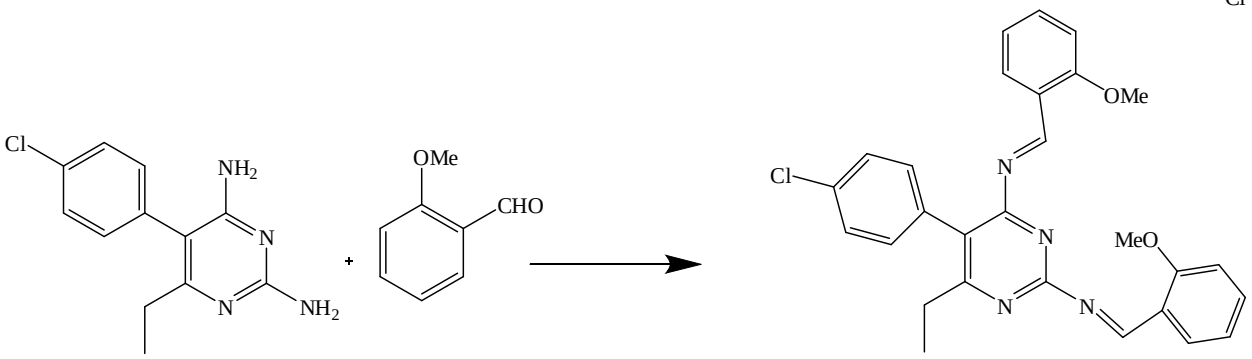


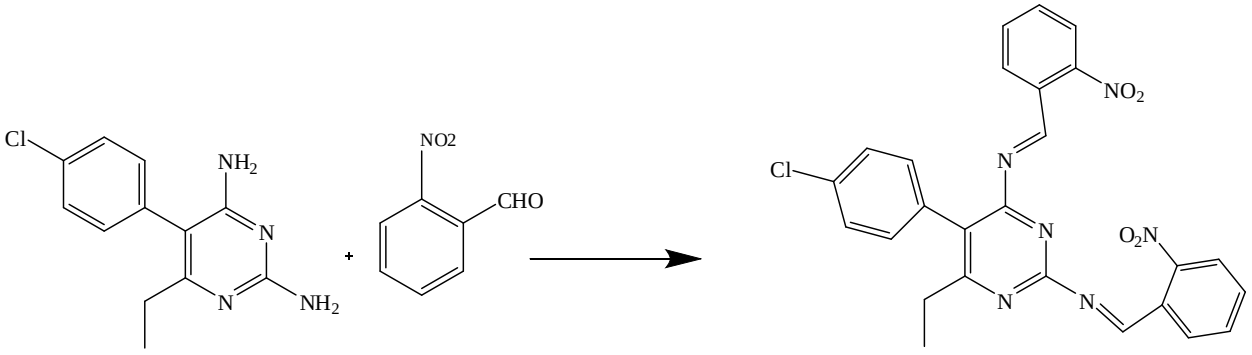


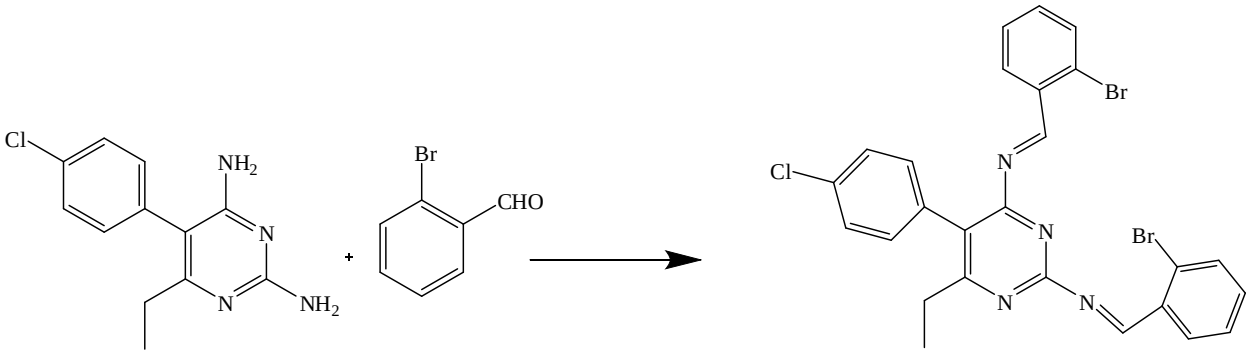
Pyrimethamine







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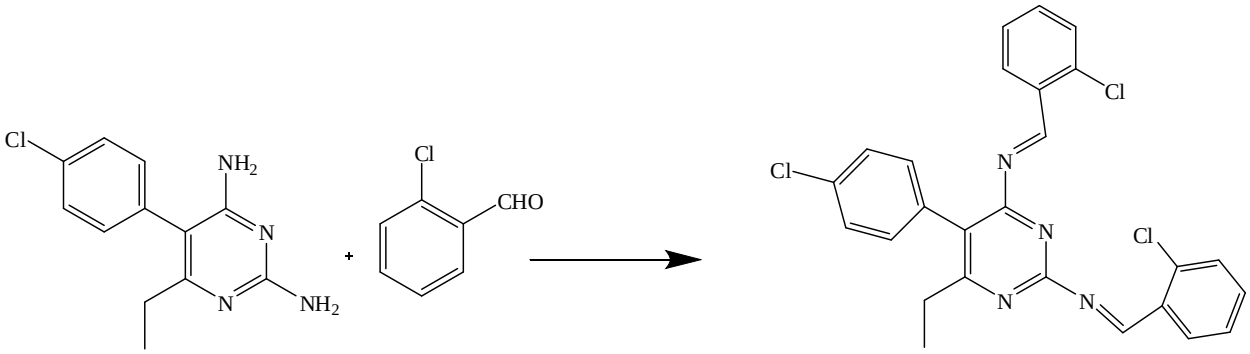
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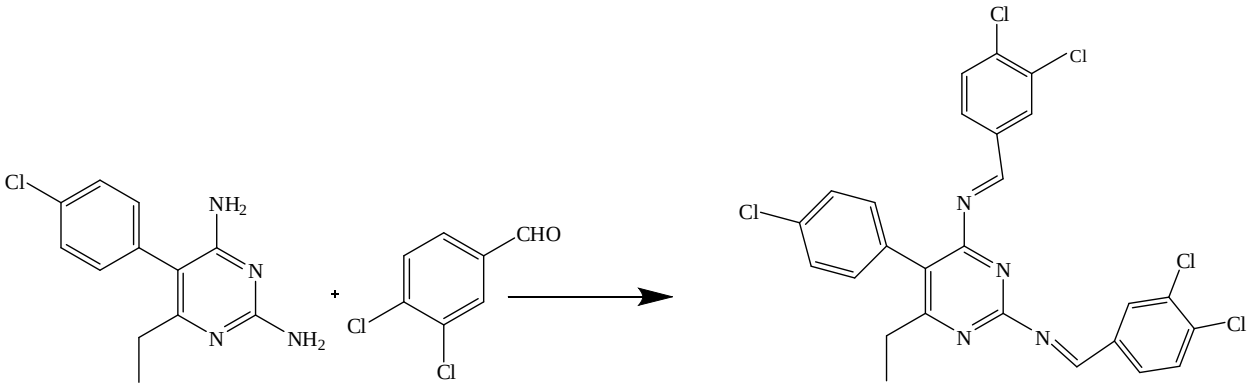
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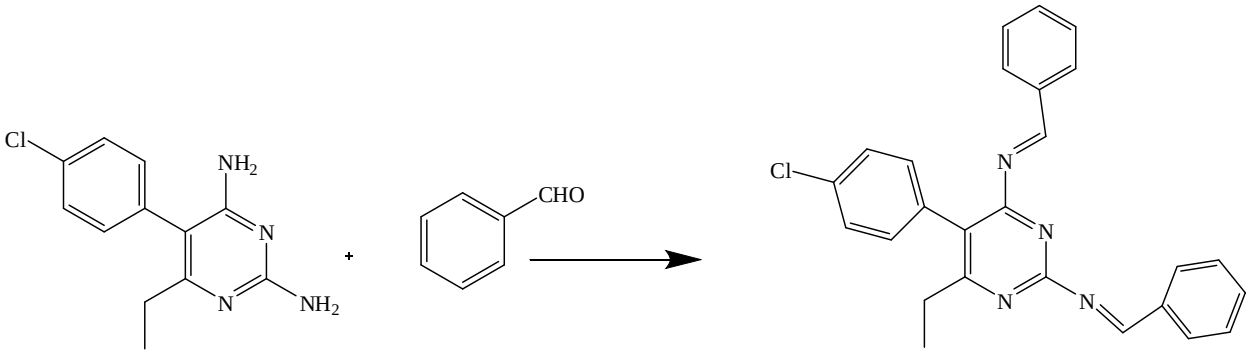
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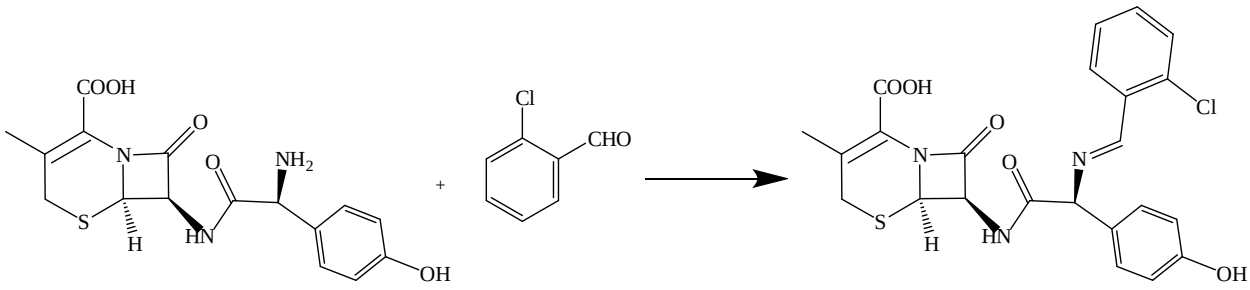
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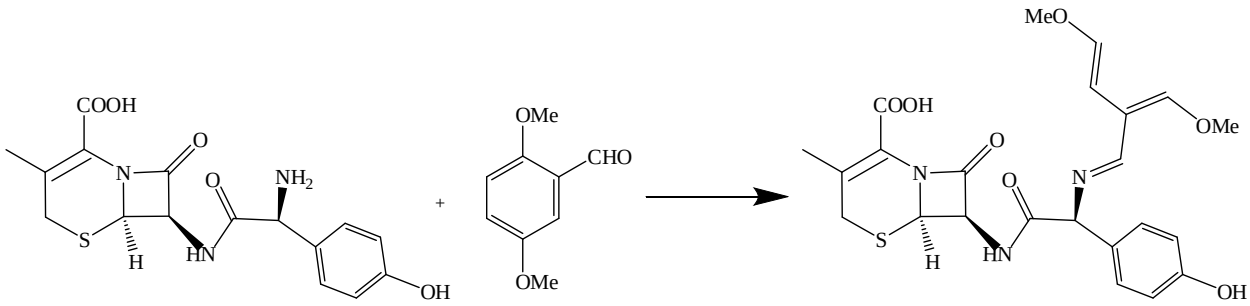
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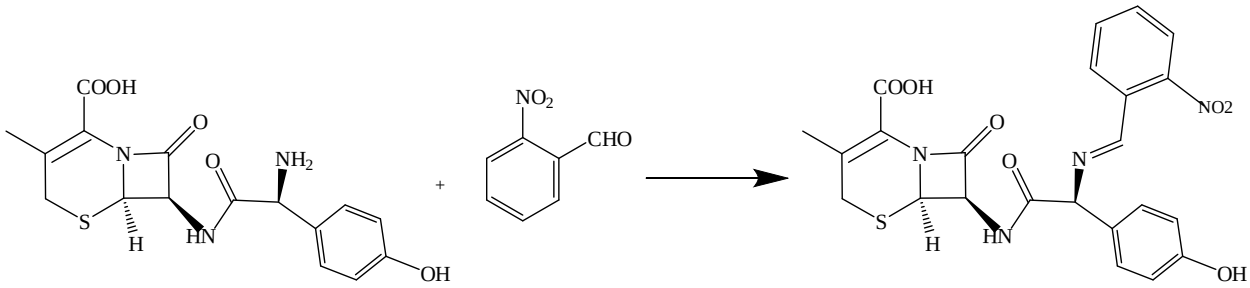
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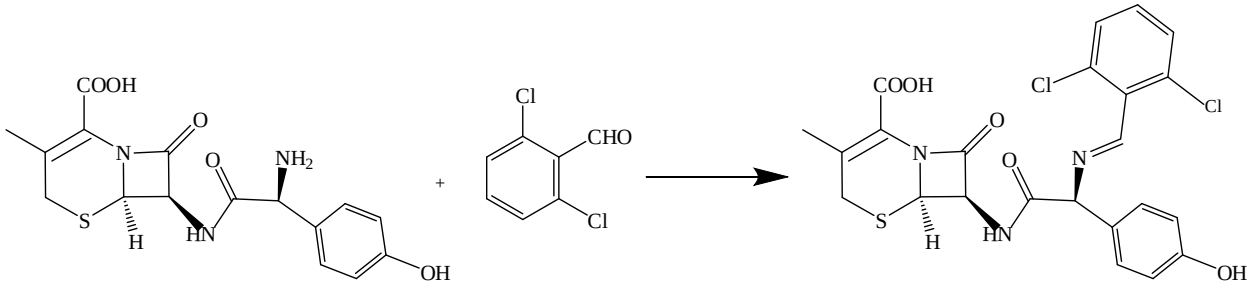
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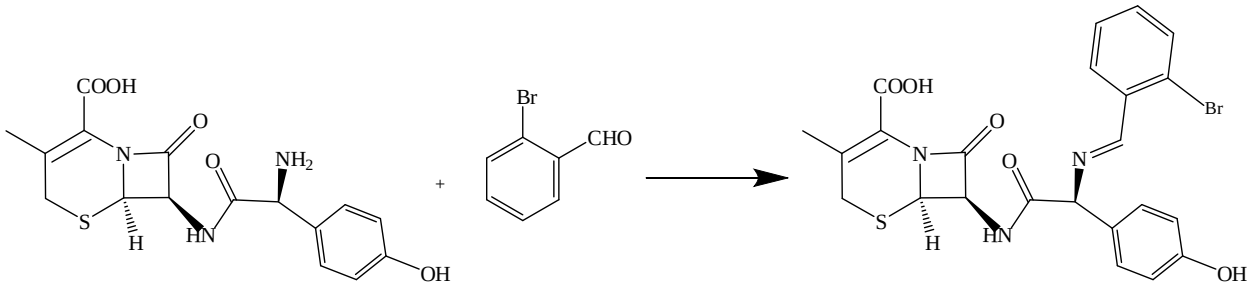
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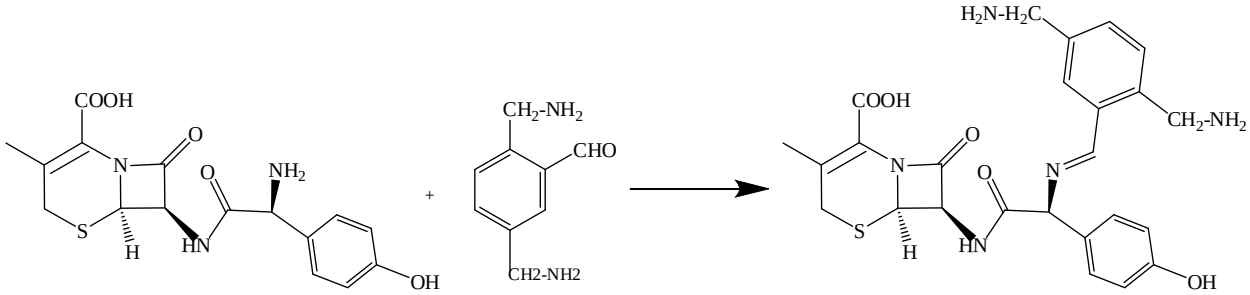
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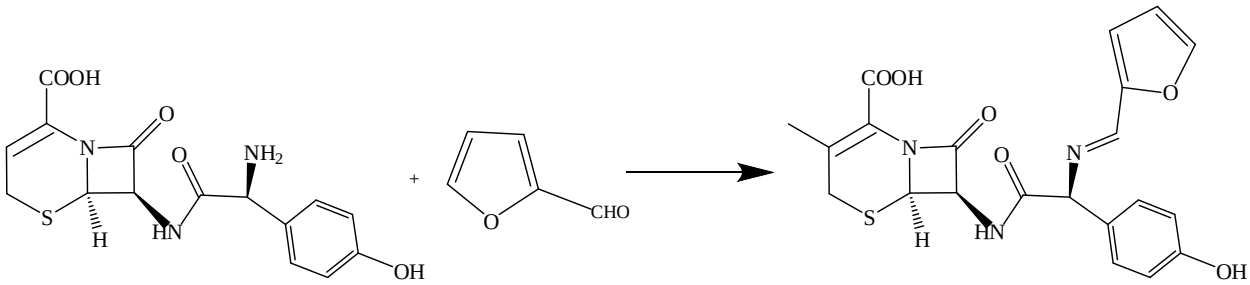
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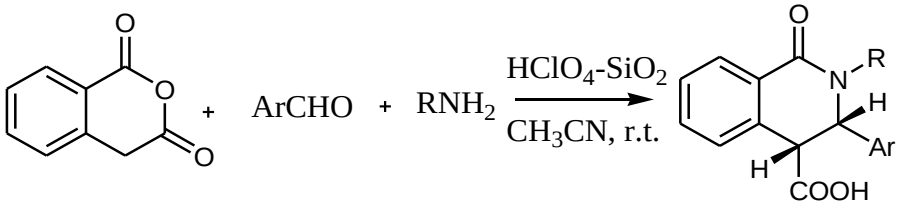
Chapter 3:- Synthesis of *cis*-isoquinolonic acids.

This chapter deals with the per chloric acid-silica catalyzed synthesis of *cis*-isoquinolonic acids. Generally, the tetrahydroisoquinolonic acid derivatives are prepared by the condensation of imines with cyclic carboxylic anhydrides[26].

Combinatorial chemistry is now routinely applied to find novel biologically active compounds. In this context, multicomponent reactions (MCRs) are powerful tools in the modern drug-discovery process in terms of finding leads and optimization[27]. The range of easily accessible and functionalized small hetero cycles is rather limited. The development of new, rapid, and robust routes toward focused libraries of such hetero cycles is therefore of great importance.

In this chapter synthesis of variety of *cis*-isoquinolonic acids using catalytic amount of per chloric acid-silica[28] was described. The treatment of homophthalic anhydride (**1**), benzaldehyde (**2**) and aniline (**3**) in acetonitrile in presence of per chloric acid-silica at ambient temperature afforded the corresponding *cis*-isoquinolonic acid derivative (**4**). (Scheme 2).

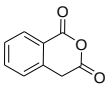
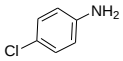
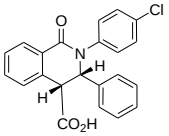
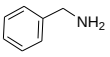
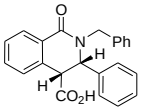
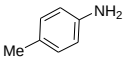
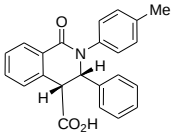
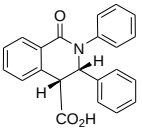
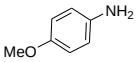
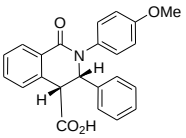
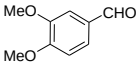
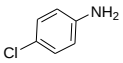
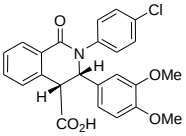
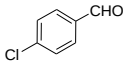
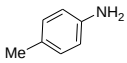
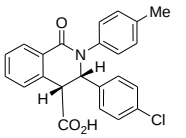
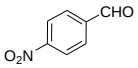
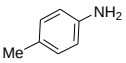
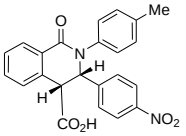
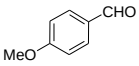
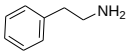
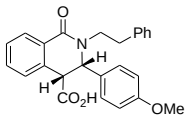
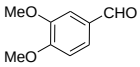
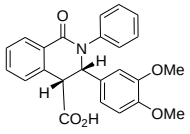
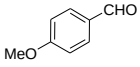
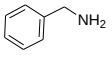
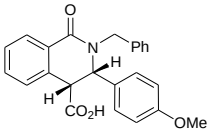
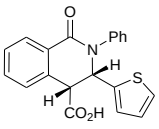


1 **2** **3** **4**

Scheme 2

Similarly, several aryl imines (generated in situ) reacted well with homophthalic anhydride to give the corresponding isoquinolonic acids in good yields. In all cases, the reactions proceeded smoothly at room temperature under mild conditions. The reactions were clean and the products were obtained in good yields and with high diastereo selectivity as determined from the NMR spectrum of the crude product. In all reactions, the product was obtained as a *cis*-diastereomer. Here, we described a simple, mild and efficient protocol for the synthesis of *cis*-isoquinolonic acids *via* three-component one-pot condensation of aldehydes, amines and cyclic enol ethers using per chloric acid-silica as catalyst.

Table 2: perchloric acid-silica catalyzed preparation of cis-isoquinolonic acids

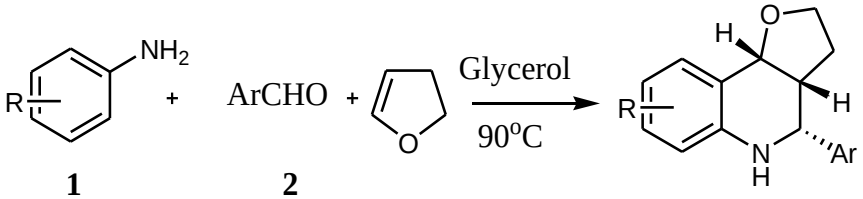
Entry	Homophthalic anhydride	Aldehyde	Amine	Product	Time (h)	Yield (%)[a]
a					6.2	80
b	"				6.1	84
c	"				6.4	81
d	"				7.0	79
e	"				6.2	82
f	"				6.0	85
g	"				6.0	80
h	"				7.5	74
i	"				6.0	90
j	"				6.4	87
k	"				6.0	90
l	"				5.5	85

Chapter 4:- Glycerol catalyzed synthesis of tetra hydro pyrano and furano quinolines.

This Chapter describes the of tetra hydro pyrano and furano quinolines catalysed by Glycerol. In recent years, Glycerol has emerged as an economically and secure solvent for organic synthesis. Glycerol is main by-product in biodiesel production and available plenty at low cost has gain importance in recent years as a reusable reaction medium for organic transformations[29].

Generally the pyranoquinoline and furanoquinoline derivatives are prepared by aza-Diels-Alder reactions[30] of imines (derived from various aromatic amines and aromatic aldehydes) with different dienophiles like 3, 4-dihydro-2*H*-pyran and 2, 3-dihydrofuran in the presence of different acid catalysts. However, many of these reactions cannot be carried out in a one-pot operation with carbonyl compound, amine and enol ether because the amines and water that exist during imine formation can decompose or deactivate the Lewis acids.

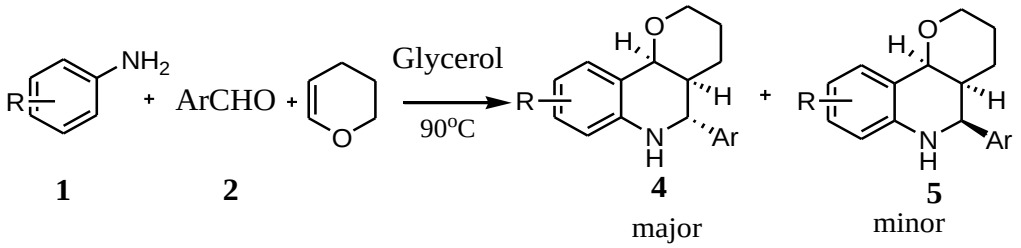
The treatment of anilines **1** and benzaldehydes **2** with 2, 3-dihydrofuran (DHF) in the presence of Glycerol at 90^{o}C afforded the corresponding furanoquinolines **3** in high yields (scheme 3).



1 **2** **3**

Scheme 3

In a similar manner, treatment of anilines **1** and benzaldehydes **2** with 3, 4-dihydro- 2*H*-pyran (DHP) in the presence of Glycerol afforded the corresponding pyranoquinolines **4** and **5** in high yield (Scheme 4).



1 **2** **4** major **5** minor

Scheme 4

Several aldimines (formed *in situ* from aromatic aldehydes and anilines in presence of glycerol reacted smoothly with 2, 3-dihydrofuran and 3, 4-dihydro-2*H*-pyran to afford the

Table 3: Glycerol promoted synthesis of pyrano, furanoquinolines

Entry	R	Ar	Olefin	Reaction time (h)	Yield [a] (%)	endo:exo[b]
a	H	C_6H_5		2.5	91	-
b	3,5-$(MeO)_2$	4-FC_6H_4	"	3.0	87	-
c	H	4-$MeOC_6H_4$	"	2.5	90	-
d	4-Me	4-ClC_6H_4	"	3.0	85	-
e	4-MeO	4-FC_6H_4	"	3.5	82	-
f	H	4-FC_6H_4	"	3.0	92	-
g	H	C_6H_5		2.5	90	92:8
h	4-MeO	C_6H_5	"	3.0	90	86:14
i	2-Me	C_6H_5	"	2.5	87	85:15
j	4-F	C_6H_5	"	3.0	86	85:15
k	4-Me	C_6H_5	"	3.0	86	87:13
l	1-Naphthyl	C_6H_5	"	3.5	82	82:18
m	1-Naphthyl	4-FC_6H_4	"	4.0	81	80:20
n	H	4-ClC_6H_4	"	3.8	85	86:14

a: Isolated and unoptimized yields
b:Cis/trans-isomers were separated by column chromatography

Corresponding furano- and pyranoquinolines in good to excellent yields. Here, we described a simple, mild and efficient protocol for the synthesis of *trans*-fused furano- and pyranoquinolines *via* three-component one-pot Aza Diels-Alder reaction of aldehydes, amines and cyclic enol ethers using Glycerol.

Chapter 5:- Synthesis of β-Amino carbonyl compounds.

The Aza Michael reaction is widely recognized as one of the most important carbon-nitrogen bond forming reactions in organic synthesis[31]. In general, this transformation is a heteroatom (nitrogen) nucleophilic (donor) addition to a β-carbon of electron-poor alkenes (acceptor) giving a stabilized carbanion intermediate, which after protonation with another electrophile furnishes the final addition product. The obtained β-amino ketones are versatile intermediates for the synthesis of various complex natural products, antibiotics, β-amino alcohols and chiral auxiliaries.[32]

These reactions are usually carried out under basic or acidic conditions. However, to avoid the side reactions, encountered in the presence of strong acid or base, a number of alternative methods have been developed. In the past years Lewis acids such as metal halides, metal triflates and microwave accelerated reactions have been shown as the best promoters for these addition reactions, especially concerning the simplicity, economy and atom efficiency aspects.

The conjugate addition of benzyl amine **1** to ethyl acrylate **2** in dichloromethane was carried out in presence of silver triflate[33] to afford ethyl (*N*-benzyl amino)-propionate **3** in 96% yield (Scheme 5).

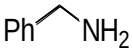
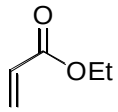
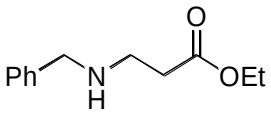
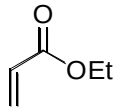
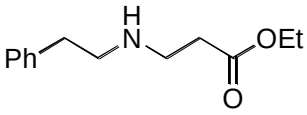
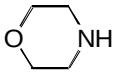
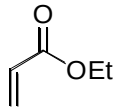
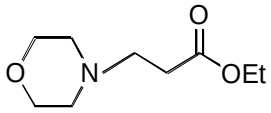
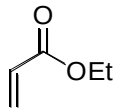
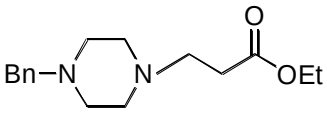
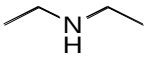
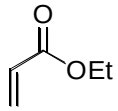
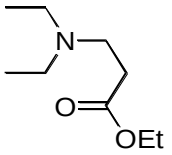
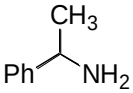
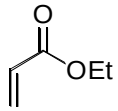
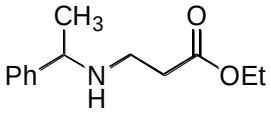
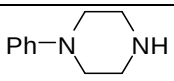
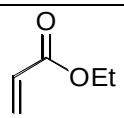
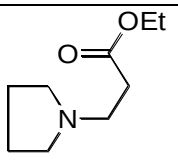
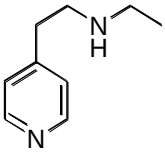
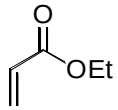
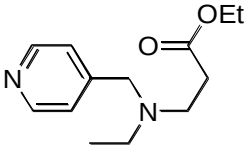
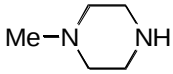
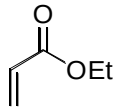
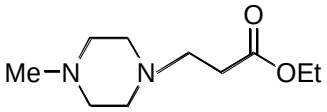
1 **2** **3**

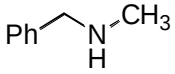
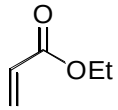
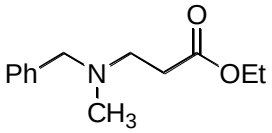
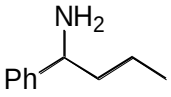
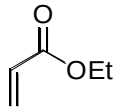
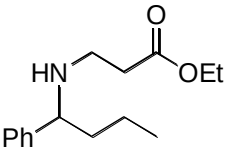
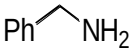
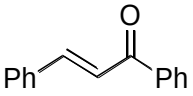
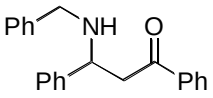
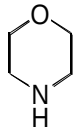
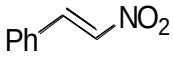
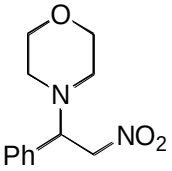
Scheme 5

Encouraged by the results obtained with benzyl amine, we turned our attention to aliphatic amines, heterocyclic amines and aromatic amines, with various α, β-ethylenic compounds. The various α, β-ethylenic compounds, such as acrylates, acrylonitrile, alkyl vinyl ketones underwent 1, 4-addition with a variety of amine nucleophiles to furnish the corresponding β-amino

compounds. Here, we have demonstrated an efficient and improved protocol for the conjugate addition of various amines to electron-deficient olefins to produce the β-amino compounds using silver triflate.

Table 4:- Silver triflate catalysed aza Michael addition.

Entry	Nucleophile	Olefin	Product	Reaction Time (h)	Yield (%)
a.				2.2	95
b.				2.8	93
c.				3.0	90
d.				3.2	92
e.				1.8	95
f.				2.5	88
g.				1.8	90
h.				2.5	88
i.				2.6	90

j.				3.0	92
k.				2.8	89
l.				3.2	85
m.				2.8	86

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